In this chapter we will consider more broadly the relationships between fMRI and other methods used to study brain function. We adopt the perspective of a neuroscientist whose interest lies not in the technical intricacies of specific methods but rather in using those methods to understand brain function. No single technique yet available (even one as multifaceted and powerful as fMRI) can fully elucidate the perceptual, motor, and cognitive processes within the brain. All techniques have weaknesses that limit the scope of their interpretative power. Indeed, one important motive for this book has been to clarify the limitations and challenges of fMRI as it is currently practiced. To overcome the weakness of individual techniques, students of brain function should employ converging operations in their research programs. That is, they should bring corroborating and complementary evidence from multiple techniques to answer a single research question. We will first consider the discipline of cognitive neuroscience generally, and functional brain mapping in particular. Then, we will describe the main techniques that have been used in concert with fMRI. Roughly considered, these techniques fall into one of two classes: manipulation techniques that change how the brain functions, and measurement techniques that observe brain function as it occurs. Throughout, we will emphasize that no matter how advanced the methods, it is ultimately the precision of the research question that determines the rate of scientific progress.

Cognitive Neuroscience

Cognitive neuroscience seeks to understand how complex behavior is produced by the functional repertoire of the brain. Like cognitive science, it studies mental processes that mediate between sensory input and expressed behavior. Like neuroscience, it seeks mechanistic explanations for behavior in the activity of neurons and in the context of evolution. Given these disciplines of origin, one straightforward strategy for cognitive neuroscientists would be to use fMRI and other neuroimaging techniques to identify the brain regions associated with the mental processes identified by cognitive science. Once the converging operations The use of two or more techniques to provide complementary evidence used to test an experimental hypothesis or scientific theory.
region that supports a given process is identified, its underlying neural circuitry can be studied in greater detail (perhaps using molecular, neurophysiological, or computational methods). If only brain mapping were so easy!

While the strategy introduced in the previous paragraph is purposefully oversimplified, it captures much of the logic used by many cognitive neuroscience studies. Is there anything unreasonable about this simple approach? A first problem concerns the questionable biological reality of the postulated mental processes, or constructs, to be studied. Many cognitive scientists are attracted to functional neuroimaging precisely because it seems to provide the means to validate abstract psychological constructs. That is, if an experimental manipulation alters a postulated construct and changes brain activity, then the construct is assumed to exist. However, there is rarely any direct evidence that a psychological construct exists as a biological entity. Indeed, a model of a cognitive process may have considerable explanatory power even though none of its parts correspond to real brain regions or measurable patterns of brain activity.

The history of science is replete with psychological constructs that were once dominant but have been discredited and forgotten. Imagine that fMRI were available in Gall’s time. Would it have made sense to conduct an fMRI experiment to search for neural activity associated with the pith, a phrenological faculty associated with one’s personal vanity? Or imagine that fMRI were available in Vienna in 1920. Would it have made sense to conduct an fMRI experiment to search for the neural locus of the id? Imagine that fMRI is available in your laboratory now. Does it make sense to conduct an fMRI study to search for the neural substrate of working memory, or altruism, or emotional intelligence? At one time or another, a wide array of constructs have been used to explain complex behavior. Some are no longer credible, others are hotly debated, while others still have widespread currency.

A second potential problem results from assuming that a unitary psychological concept must be realized by a unitary biological entity. One might conclude, on the basis of a blob of active voxels found using fMRI or a new component identified using electrophysiology, that a construct as abstract and multifaceted as emotional intelligence is actually a discrete brain process controlled by a particular part of the cortex. Yet this is unlikely to be the case. Complex constructs probably emerge from the coordinated activity of more basic functions, and the mapping of any complex construct to a single, discrete anatomical focus seems improbable.

Third, the course of neural activity need not be isomorphic with the presumed behavior of the construct. Does increased attention have to be manifest as an increased BOLD signal? Or could attention decrease BOLD activation in a brain region? Does maintaining a memory over a 20-s period require neurons to continually fire for 20 seconds? While many fMRI statistical analyses assume isomorphism between stimuli and the measures of brain function they evoke, this assumption may be wrong under many circumstances.

Fourth, the very nature of most physiological methods in cognitive neuroscience ensures that researchers find evidence for localization of function. All of the many techniques discussed in this chapter provide data about spatially differentiated functions. A cognitive function that was equally distributed throughout the brain would be nearly invisible to the physiological techniques described in this book. In recent years, the advent of functional connectivity techniques in fMRI—along with the simultaneous development of multielectrode recording approaches in non-human electrophysiology—has begun to provide information about larger networks of brain function. Even so, it is not

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**construct** An abstract concept that explains behavior but which itself is not directly observable. Attention is an example of a psychological construct.

**isomorphic** Having an identical form. A physiological measurement that is isomorphic with a psychological construct would vary over time consistently with the postulated changes in the construct.

**localization of function** The idea that the brain may have distinct regions that support particular mental processes.

**functional connectivity** A pattern of functional relationships among regions, inferred from common changes in activation over time, that may reflect direct or indirect links between those regions.
surprising that most cognitive neuroscience studies conclude that some psychological construct is localized to a small set of spatially discrete regions.

Finally, investigators often implicitly assume that, within some limits, functions are localized in the same brain regions of different individuals. In many fMRI studies, great effort is expended to normalize each individual's brain anatomy to a common standardized brain space or atlas (see Chapter 8). Normalization improves the statistical reliability of the inferences we draw from imaging data, while reassuring scientists who are suspicious of single observations. Similar methods have been devised to standardize electrophysiological and lesion data into common coordinate systems. While normalization methods have been extraordinarily useful for many research questions, they are not appropriate for brain functions that are located in different regions in different individuals. For example, the hemispheric laterality of language can vary with handedness or as a result of early brain injury. If a subject group contained some left-handed and some right-handed individuals, a group statistical analysis might reveal bilateral activation even though each subject had a highly laterialized pattern. Therefore, when studying questions related to language function, investigators often attempt to minimize suspected differences in brain organization by selecting only right-handed subjects.

**Strategies for research in cognitive neuroscience**

In contrast to the idealized strategy discussed earlier in this chapter, the real practice of cognitive neuroscience is messy and incremental. A research hypothesis may be initiated by a concept from psychology, such as the distinction between short-term and long-term memory. Or, the idea may come from a neurological observation, for example, that bilateral lesions of the medial temporal lobe lead to a permanent disability to create new memories. Following the initial hypothesis is a cycle of testing, refinements of the hypothesis, and more testing.

Physiological data, and in particular fMRI, can play an important role in this iterative process, by breaking down complex behavior into functional components. One strategy is to assume that activation at different anatomical loci or at different temporal latencies reflects different cognitive processes. Following this logic, if you run the perfect experiment to isolate your favorite psychological construct, and you reliably identify several discrete foci of activity, then you conclude that your construct must have several components. You can then perform additional experiments to try to dissociate these components on the basis of psychological manipulations. A related strategy reverses the emphasis. You can test a wide range of experimental manipulations to see which alter the activity of a single brain region. To what stimuli is this area sensitive? Does its activity change with learning? Must a stimulus be attended to for activity to be evoked, or is activity evoked automatically? How does activity change if the subject is given extensive training with the stimuli?

By continually testing and revising hypotheses about brain function, cognitive neuroscientists can help transform an ill-defined psychological construct into a clear theory whose components are associated with specific brain structures. Conversely, psychological concepts can shape the course of cognitive neuroscience by indicating important areas for research. In the following sections, we describe the various techniques used by cognitive neuroscientists to test their hypotheses. Within each section, we describe the technique, its applications, and its integration with fMRI research. We hope to convey how converging studies using these seemingly disparate techniques provide the best opportunity for advances in our understanding of brain function.
Manipulating Brain Function

Some research techniques are direct: they quantify changes in the world caused by an experimental manipulation. For example, if you are interested in the effects of an induced magnetic field on the voltage across a wire, you can collect data using a voltmeter attached to electrodes on the wire. Similarly, you can place electrodes directly on the brain surface to measure voltage changes associated with neuronal activity. Other methods are indirect and collect data about something correlated with, but not necessarily caused by, the process of interest. Most brain imaging methods, including fMRI, provide indirect measures of neuronal activity. If the correlation between the measured process and the process of interest is high and reliable, then an indirect method can be very valuable. However, if these processes are only weakly correlated, or can be dissociated by other (often unknown) processes, then the value of an indirect technique is diminished.

For research questions about psychological constructs, all techniques for measuring brain activity are indirect (see Figures 9.3 and 9.4). Even when neuronal activity is measured directly using certain electrophysiological techniques, it does not necessarily reflect the psychological construct of interest. For this reason, neuroimaging and electrophysiological techniques are commonly criticized as revealing correlations, not causes. That is, while they can demonstrate an association between a brain region and a psychological construct, they cannot establish that the brain region is necessary for the construct. As an example: If an investigator demonstrates with fMRI that the performance of a working memory task activates a specific region of the dorsolateral prefrontal cortex, would the removal of that region of the cortex (or, less drastically, the elimination of its activation) impair working memory? To answer questions about necessity, cognitive neuroscientists must manipulate the brain in some way and then assess the effects of that manipulation on behavior.

Direct cortical stimulation

An extremely important technique for establishing the necessity of a brain region for a cognitive construct is cortical stimulation, or the application of an electrical current to evoke neuronal activity. Three primary stimulation techniques are in use today. In direct cortical stimulation, electrical current is introduced using relatively large electrodes that are placed on the surface of the brain, directly into the brain tissue, or even on the surface of the scalp. Many modern animal studies use microstimulation techniques that activate only a small number of neurons. For studies in volunteer human subjects, the introduction of a focal magnetic field from outside the skull, through a process known as transcranial magnetic stimulation (TMS), evokes activity in neurons within a large brain region.

The first scientific studies of direct cortical stimulation were reported in the 1870s, during a period of transition in neuroscience. Before this time, the dominant concept of brain organization had been the idea of equipotentiality, that cognitive functions were equally distributed throughout the cortex. This idea had been based largely on the work of the French physiologist Pierre Flourens, who created lesions in the brains of rabbits and pigeons and then observed their behavior. Lesions in subcortical structures caused specific behavioral deficits (e.g., lesions in the medulla impaired respiration), but damage to the cortex was never functionally specific. Based on these results and those from other laboratories using other species, Flourens became a vocal opponent of the idea of local-
Gall; see stimulation colleagues methodi­infuenti.ll Jasiorkowski.) milppt."d on the contralateral side. Stimulation of other brain flow. Montrei11 NeurologiCClI David Spencer, Y,llt' University; pulses, m<lp areas dogs caused of stimulation on the function(s) of interest, while to func­ who helped Hitzig stimulating e1edrodes and SOUI'Cl.' to motor cortices, to patient between from motor, Ian the leave critical OIl'eas includ­of the Fllllclio/! surgery while ilwake. the surfatt polir cooperative during tbilt pi'lrt deep effect of electrical current, comprehension, awaiting positive undergoing stimulation, circumscribed left front,lllesion. that the book as SIRG'SOl'OIl's the {Courtesy and D. the American-born direct the a resection. of the procedure. Some corti­brain in of it is then the cortex in surgery. a surgeon places moves functions ~IS anode abov­it itself. and Eduard the the<br>brain's cortex, of function the British scientist and a source free ck'Ctrons. is placed on the surface of the cortex (Figure 13.1 A). One electrode, such a (If evidence in favor of cor­the exposed Broca's 1861 observation of aphasia (i.e., an inability to speak) caused by a circumscribed left frontal lesion. Within this changing climate, the German physiologists Gustav Fritsch and Eduard Hitzig reported that direct cortical stimulation of anterior regions of the cortex in dogs caused muscular movements on the contralateral side. Stimulation of other brain regions produced no such movement. Their results precipitated an explosion of interest in cortical stimulation, and researchers such as the British scientist David Ferrier soon mapped large regions of the sensory and motor cortices. By the 1876 publication of Ferrier's influential book The Function of the Brain, evidence against equipotentiality had become overwhelming.

Today, direct cortical stimulation is most frequently used to map areas of critical function (e.g., language, motor abilities) in patients awaiting or undergoing neurosurgery. Based on the functions of brain regions located near the surgical target, neurosurgeons may change the path taken through the brain surface in order to leave critical areas intact while removing a deep tumor, or they may remove more or less tissue during a resection. This minimizes the chance that the patient will suffer from motor, language, or other deficits as a result of the surgery. An early pioneer of this approach was the American-born neurosurgeon Wilder Penfield, who helped found the Montreal Neurological Institute. During the 1940s and 1950s, Penfield and his colleagues methodically mapped the human brain in patients undergoing surgery while awake. In addition to the sensory and motor cortices, Penfield studied brain regions involved in language processing and memory. Within the discipline of neurosurgery, direct cortical stimulation remains the standard procedure for functional brain mapping.

In the modern practice of direct cortical stimulation, a pair of stimulating electrodes is placed on the surface of the cortex (Figure 13.1A). One electrode, designated the anode, provides the source of electrical current, while the second electrode, designated the cathode, provides the sink to which the current will flow. The stimulation usually consists of weak (1 to 10 μA) current pulses, rapidly presented (e.g., 50 Hz), each of 100 to 500 μs duration. During stimulation, brain tissue in the current path between the anode and the cathode is depolarized. Stimulation mapping is often conducted during the surgery itself. The surgeon moves the electrodes to different locations on the exposed cortical surface, tests the effect of stimulation on the function(s) of interest, and then places numbered sterile paper tickets on the cortex, as markers of function (Figure 13.1B). If sensory or language functions are being tested, the patient needs to be awake and cooperative during that part of the procedure. Some

**Figure 13.1 Direct cortical stimulation.** In some neurosurgical procedures, it is important to localize particular functional brain regions that might be located near the planned excision. In direct cortical stimulation performed during surgery, a surgeon places a pair of stimulating electrodes on the surface of the brain while testing the patient for language comprehension, speech, sensation, or movement. In (A), the surgeon's gloved hand can be seen holding the cathode and anode above the brain's surface. In (B), functional areas of the brain are marked by sterile tickets that indicate what function was evoked or interrupted at that site. (Courtesy of Dr. Dennis D. Spencer, Yale University; photographs by Joseph Jasiorkowski.)
muscular twitches evoked by stimulation can be observed with patients who are under light anesthesia.

In patients with some forms of epilepsy, grids of electrodes are sometimes implanted subdurally over a period of days or weeks (Figure 13.2). The grids are typically constructed of a flexible sylastic sheet into which small electrodes are embedded. A typical grid may consist of an 8 by 8 array of electrodes, each separated by 1 cm and therefore covering a 49 cm² area of cortex. By recording the frequency and locations of seizures within this grid, the patient’s doctors can determine whether a particular surgical excision would reduce seizure frequency or eliminate the seizures entirely. In these circumstances, direct cortical stimulation mapping is sometimes performed using these electrode grids. Electrical current is systematically introduced between adjacent pairs of electrodes while the subject is engaged in a language, motor, or perceptual task. Since patients are conscious, alert, and comfortable during these extraoperative stimulation studies, much useful information has been obtained about higher cognitive function from these procedures.

**Functional consequences of direct cortical stimulation**

The consequences of direct cortical stimulation differ for different brain regions. Stimulation in some locations evokes a positive response; for example, stimulation of the hand region of the primary motor cortex might evoke flexion of the fingers on the contralateral hand, while stimulation of the mouth region may cause the lips to twitch or the tongue to move. Positive responses provide particularly strong evidence for the causal role of a brain region in an action or percep. In other regions, stimulation might cause a negative response: it inhibits activity. Stimulation of a small region of the left inferior frontal region (i.e., Broca’s area) can cause speech arrest, even though patients can still move their mouths and tongues on command. After the stimulation ends, patients report that they knew what they wanted to say but were unable to say it. During stimulation of Wernicke’s area in the posterior temporal cortex, patients remain able to speak but they may not be able to understand the speech of others, carry out spoken commands, or complete simple sentences. Or, stimulation may have no effects at all. This may occur because the current density was too weak to depolarize nearby neurons, in which case increasing the current may yield a response. It may also result from a failure to test the specific process supported by that region. For example, as described in the following paragraph, stimulation of some regions of the fusiform gyrus in the temporal lobe produces an inability to recognize familiar faces while preserving the ability to name familiar objects. An investigator who never presented images of faces during stimulation might mistakenly conclude that the fusiform gyrus was functionally silent.

Sometimes both positive and negative effects can be obtained by stimulation at the same site. Stimulation of the supplementary motor area can evoke both simple and complex coordinated motor actions. It can also disrupt ongoing motor activity that requires bimanual coordination, such as twiddling one’s thumbs. A striking example of both positive and negative effects of stimulation comes from a 1999 study by Puce and colleagues, who stimulated electrode sites on intracranial grids within the fusiform gyrus. Before stimulation, the researchers showed the subjects photographs of familiar and famous faces of people the subjects were able to identify. The faces, but not other stimulus categories, evoked large changes in electrical potential in electrodes within the fusiform gyrus. The investigators then stimulated those electrodes. Several of
the subjects became prosopagnosic during the duration of the stimulation; that is, they could no longer recognize the faces, although they could recognize common objects. When the stimulation ended, they could once again recognize the faces. While the disruption of face recognition by stimulation was a noteworthy finding, there was the possibility that the effect was not specific to faces. Perhaps the disruption would also have occurred for any object that had a specific ellipsoidal shape, had bilateral symmetry, or was in the general category of living things. However, in two of the subjects, stimulation evoked a vivid hallucination of a face. This remarkable positive effect of stimulation provided strong evidence that the observed disruption was specific to faces.

While direct cortical stimulation is a potentially powerful technique, it has several limitations. First, it is invasive and may precipitate a seizure, particularly in patients who suffer from epilepsy. This risk means that direct cortical stimulation can only be performed as part of a clinical procedure. Second, at high electrical currents that are sufficient to depolarize neurons, the current may spread from the stimulating electrodes and excite brain regions some distance away. This can introduce uncertainty in the interpretation of the localization results. For this reason, the cathode and anode are usually kept in close proximity, and the investigator gradually increases the stimulating current so that the threshold at which a stimulation effect is first observed can be monitored. Third, positive or negative effects of stimulation do not necessarily indicate that the surgical removal of the stimulated region will cause corresponding deficits. For example, a 1986 stimulation study by Luders and colleagues found that stimulation of part of the left fusiform gyrus can lead to an inability to speak or understand language. Despite these striking deficits, surgical removal of this region does not typically cause the same severe and lasting language deficits that follow removal of Wernicke’s or Broca’s areas. Why does damage to some brain areas lead to functional deficits, while damage to others results only in mild or transient deficits? As we will consider in the discussion of lesion studies later in the chapter, this may reflect the ability of the brain to reorganize some functions following damage, perhaps by engaging homotopic regions in the opposite hemisphere.

Several studies have directly compared cortical stimulation with fMRI. In 1999, Schlosser and colleagues tested patients who were about to undergo surgery in the language-dominant temporal lobe. To help guide the neurosurgeon, localization of temporal lobe language regions was attempted preoperatively using a blocked-design fMRI study in which native English-speaking subjects passively listened to speech that alternated between familiar (English) and unfamiliar (Turkish) languages. The same speaker was used throughout, and basic auditory properties were controlled between the two conditions. Greater activation was observed in response to the English speech in the lateral temporal (i.e., Wernicke’s area) and inferior frontal (i.e., Broca’s area) cortices in the language-dominant hemisphere of most subjects tested. Direct cortical stimulation was also used to localize the lateral temporal language region in some subjects. At electrode locations near the locations of fMRI activity, cortical stimulation interfered with auditory comprehension, object naming, or speech production tasks in nearly all subjects. Stimulation therefore validated the results obtained from the fMRI task. However, while the correspondence between temporal lobe language areas identified by fMRI and by direct cortical stimulation was generally good, differences were noted in the spatial extent of activation using these different methods.

As noted in Chapter 7, the spatial extent of fMRI activation may overestimate the area in which neuronal activation occurs, and so these methods may
single-pulse TMS The delivery of a single TMS stimulation pulse, in order to disrupt some ongoing brain process.

repetitive TMS (rTMS) The delivery of an extended series of closely spaced TMS stimulation pulses, in order to effect long-lasting changes in brain function.

Transcranial magnetic stimulation (TMS)

So far in this chapter we have discussed invasive methods for direct cortical stimulation that involve opening the skull to place electrodes against the brain. An alternative and less-invasive method, transcranial magnetic stimulation, was introduced in the 1980s. In TMS studies, an electrical coil is placed on the outside of the skull and rapidly charged with current (Figure 13.3A). This generates a strong magnetic field (as large as several Tesla) that lasts less than a millisecond. This field extends through the skull and into the brain (Figure 13.3B), where it produces an electrical current in local axons by electromagnetic induction. The configuration of the coil influences the focality of the field and, thus, the spread of the electrical current. One popular coil design has the shape of a figure eight, for which the field is maximal near the midway point between the coils.

Researchers use TMS in either of two ways: to deliver a single brief electrical pulse to the brain (single-pulse TMS), or to deliver a series of pulses over a period of minutes (repetitive TMS, or rTMS). Note that we consider intermediate approaches involving short bursts of pulses over a few seconds to be within the general category of single-pulse TMS, given that they share conceptual underpinnings. These two approaches differ in their effects on brain function. Single-pulse TMS first evokes a brief (−10 ms) burst of neuronal activity, perhaps reflecting evoked activation in local neural circuits, then leads to a longer interval (−200 ms) of relatively suppressed neuronal activity. Single-pulse TMS thus causes a very transient disruption of an ongoing process. Repetitive TMS can cause long-term effects (e.g., lasting for many minutes) on the excitability of neurons within the affected region. The neurons may become either more or less excitable, depending on the pattern of pulses delivered. Moreover, rTMS may lead to indirect changes in brain physiology, such as long-term increases in blood flow to a stimulated region. Because of the breadth of its effects, rTMS has been evaluated as a potential treatment for chronic neurological and psychiatric conditions. Despite some early promising results in
the treatment of several disorders (e.g., depression), the clinical efficacy of rTMS remains a subject of vigorous debate in the literature. For a recent and thoughtful summary, see the 2007 review article by Ridding and Rothwell cited in the chapter references.

**Thought question**

How might the physiological changes evoked by TMS mirror those evoked by rapidly changing gradients during MRI?

As currently practiced, TMS is considered a safe and noninvasive method and has been used in more than 2000 published studies of both healthy volunteers and patients. Indeed, one of the authors of this textbook was a volunteer subject in one of the first studies performed to test the safety of the single-pulse TMS method. It should be noted, however, that prior to the establishment of safe operating limits and procedures, rTMS evoked seizures in a small number of presumably normal subjects who had no prior history of epileptic activity. Also, due to the spread of the current, the actual brain regions stimulated are much more extensive than in the direct cortical stimulation studies discussed earlier (see Figure 13.3C).

TMS has been used in a large number of creative studies of brain function. By manipulating the latency at which a pulse is applied to a given brain region, researchers can interrupt processing at different points in time. For example, in 2003, Mottaghy and colleagues used single-pulse TMS to study verbal working memory in a "two-back" task (i.e., subjects viewed a series of letters and pressed a button when the current letter matched one from two trials ago). The delay between the task stimulus and the delivery of the TMS was varied over a range of 140 to 500 ms. The authors found that working memory processes were impaired by shorter-latency TMS delivered to the parietal cortex and by longer-latency TMS delivered to the frontal cortex. This suggested that the flow of information was from parietal to frontal sites. Within the frontal lobe, TMS delivered to the right hemisphere caused disruption with shorter delays than stimulation in the left frontal region, suggesting a flow of information from the right to the left hemispheres. However, delivery of TMS did not disrupt a simple control task that did not have a working memory component, which indicated that the effects of TMS in these regions were specific to working memory processes and specific to particular intervals in time. TMS can also be used to examine relatively long-distance influences between brain regions. As shown in a 2006 study by Ruff and colleagues, TMS applied to the frontal eye fields (i.e., regions of the frontal lobes that support eye movements and visual attention) modulated activation in the early regions of the visual cortex, which in turn changed the quality of visual perceptions.

One of the most promising uses of TMS has been to determine whether regions activated in fMRI studies are essential for task performance. For example, in 2002 Rushworth and colleagues used fMRI to identify regions of the frontal lobe that were activated during two forms of task switching. In the response-switching condition, subjects switched between rules for selecting a response, while in the visual-switching condition, subjects switched between rules for selecting a stimulus. For each trial in each condition, the subject either kept or switched the rule from the previous trial. Although the two conditions evoked fMRI activity in somewhat different sets of brain regions, both activated the pre-supplementary motor area (pre-SMA) region of the medial frontal cortex. The authors thus hypothesized that this region plays an important role.
in task switching. To test this hypothesis, the authors later stimulated the pre-SMA using rTMS. This disrupted both tasks, but only in trials when the subject switched from the previous task rule. When the TMS stimulator was moved over the motor cortex adjacent to the region of fMRI activity, stimulation had no effect on the task. Together with the fMRI results, these TMS data provide important converging evidence that the pre-SMA is a critical brain region in task switching, and furthermore, that its role is limited to actual task switches. While combined or parallel use of TMS and fMRI is still relatively rare, such studies provide important complementary information about the timing of brain function and causal influences on brain function.

**Brain lesions**

One of the earliest and most productive approaches for studying brain function was the observation of behavioral or cognitive changes associated with brain lesions. Shortly after Broca's 1861 discovery, many other effects of brain lesions were reported. In 1868, Dr. John Harlow described his observations of Phineas Gage, a railroad foreman in Cavendish, Vermont, who in 1848 suffered a horrible accident in which an explosive charge blasted an iron tamping rod through his left cheekbone and out of the top of his head. Gage not only survived the accident, and was able to walk and speak within minutes, but lived for another 12 years. However, according to later reports, Gage suffered from a dramatic change in personality: he became profane, irresponsible, and showed little regard for others. (A 2002 book by MacMillan paints a somewhat more complex picture of these personality changes.) Gage's was one of the first cases in which a profound alteration of personality was linked to a lesion within a specific brain region. Around that same time, early researchers such as the German neurologist Hermann Munk created controlled, experimental lesions in animals to make important discoveries about the organization of the cerebral cortex. Other scientists, like David Ferrier, used both lesion and cortical stimulation to study brain function in animals.

Lesion studies in both humans and animals remain central to cognitive neuroscience research. Like cortical stimulation experiments, which create transient and reversible impairments, lesion studies provide information about the necessity of a brain region for a particular function. However, lesion studies have several obvious limitations. Studies in humans depend primarily on naturally occurring lesions, such as those produced by strokes, which can be large and extend across many functional brain regions. This variability makes it impossible for investigators to assemble a group of patients with identical lesions. Furthermore, natural lesions often involve damage to white-matter pathways, thus impairing functions that are supported by distant brain regions that were undamaged but became disconnected. Some types of lesion can be studied in groups of patients with similar damage, as may occur with well-defined surgical lesions. An example is patients who have received temporal lobectomies to relieve intractable epileptic seizures. However, such patients may have suffered for many years from preexisting neurological disorders, and often continue to take powerful drugs that may alter normal brain function.

Lesion studies can also have interpretive difficulties. Unlike the positive results sometimes observed with direct cortical stimulation, lesions do not produce complex behaviors. Thus, the loss of function following a brain lesion does not guarantee that the damaged brain tissue was the locus for that particular function. For example, a large lesion in the primary visual cortex would impair not only basic visual perception but also many higher-order functions like object
recognition, reading, and eye gaze perception. It would be absurd to suggest that all of these visually based functions reside in the primary visual cortex, yet this region is clearly essential for every one of them. For this reason, investigators who employ the lesion approach systematically compare the effects of lesions in different brain regions on performance in various experimental tasks, in order to identify patterns of association and dissociation between brain regions.

To this end, several groups around the world have established large databases, or registries, of individuals who have brain lesions and who have been studied while performing large numbers of different tasks. For a broad overview of the registry approach, see the 2008 review article by Fellows and colleagues cited in the chapter references. One example is the Cognitive Neuroscience Patient Registry developed by Antonio and Hanna Damasio and their many collaborators at the University of Iowa. Another is the patient registry developed by Robert Knight and his colleagues at the University of California, Berkeley. These and similar registries contain both contact information and quantitative reconstructions of lesions (using structural MRI data) for large numbers of individuals with brain damage. By identifying individuals who share a particular form of damage (Figure 13.4) and testing those people using a spectrum of behavioral tasks, researchers can evaluate whether damage to particular regions contributes to changes in one or more aspects of behavior.

**Figure 13.4** Lesion maps from a patient registry. Shown are lesions in the left dorsal prefrontal cortex of eight subjects (top eight rows). The lesions are indicated by red shading on a stack of axial MRI slices and on a surface reconstruction (at right). The bottom row shows a color-coded summary that indicates the degree of lesion overlap in this sample. (Courtesy of Dr. Robert Knight, University of California, Berkeley.)
Lesion studies have considerable value for the dissection of complex tasks into their components. In 1955, Teuber introduced the concept of the double dissociation (see Chapter 11 for a discussion of its applications to fMRI). By demonstrating that a lesion in brain structure A impairs function X but not function Y, a researcher establishes a single dissociation between the functions. But with the additional result that a lesion in structure B disrupts function Y but not function X, the researcher has established a double dissociation, and can make more specific inferences about brain function. Consider the following example. An investigator creates a model for face processing based on the hypothesis that separate processes exist for retrieving face identity and for judging emotional facial expression. Then, that investigator shows that a group of lesion patients have impaired face recognition but normal ability to judge emotional expressions. Although this result is consistent with the model, it could also merely reflect that face recognition is more difficult, and thus more easily disrupted. More conclusive support for the model would come from a second demonstration showing that damage to a different brain region impairs judgments of emotional expressions but not face recognition. The book by Shallice, listed in the suggested readings, provides additional discussion of lesion interpretation in the context of neuropsychological theory, including caveats concerning double dissociation.

**Combined lesion and fMRI studies**

Evidence from lesion studies can greatly extend the interpretive power of fMRI. When a process both evokes fMRI activity in a brain region and is disrupted when that region is lesioned, researchers can more readily conclude that the process relies on that brain region for its execution. The benefits of converging lesion and fMRI studies are thus similar to those of combined direct cortical stimulation and fMRI studies, as discussed earlier.

Many studies that have combined lesion analysis and fMRI in a single individual were designed to investigate the influence of a developmental lesion on a well-localized function, such as language processing in the left hemisphere. For example, in 2002, Staudt and colleagues found that individuals who had suffered perinatal left-hemisphere lesions exhibited language-related activation in the right hemisphere. From these fMRI results, the authors argued that early damage to left-hemisphere regions that support language would result in the recruitment of homotopic regions in the undamaged right hemisphere. Another example comes from the 1997 work of Schlosser and colleagues, who studied a 19-year-old patient with a large arteriovenous malformation in her right frontal and rostral parietal lobes. Since childhood, she had poor motor control but preserved sensation in the left side of her body (i.e., hemiparesis). During an fMRI session her left and right hands were alternately stroked with a brush. Strong activation was obtained in response to both types of stimulation, but stroking the left hand activated the primary sensory region of the ipsilateral left hemisphere (Figure 13.5). That is, her brain was reorganized so that sensations from both sides of the body were (at least partially) represented in the same hemisphere. These fMRI studies provide strong evidence for the functional plasticity of the human cortex in response to early brain injury. Note that acute lesions, such as from surgery, may lead to dramatic and permanent changes in function. An intriguing recent example comes from a 2006 study by Gaillard and colleagues, who found that the surgical removal of a word-selective region in a patient’s ventral visual cortex not only altered the fMRI response to words but also led to a comprehensive reading deficit.
Combined fMRI and lesion methods have also been used to study recovery of function in individuals who acquired lesions in adulthood from stroke or other brain injury. Using fMRI, TMS, and magnetoencephalography, in 1998 Rossini and colleagues investigated changes in the brain of a poststroke patient who had recovered significant motor function. Their results suggested that the sensorimotor cortex in the affected hemisphere was enlarged, and shifted posteriorly, compared to the other hemisphere. In a similar study conducted in 1997, Cramer and colleagues used fMRI to study 10 patients who had recovered good motor function following stroke. When the patients performed a finger tapping task, activity in the sensorimotor cortex of the unaffected hemisphere was increased relative to controls. Increased activation was also found in the SMA and cerebellum. These results suggest that recovery of motor function after stroke involves the increased participation of homotopic regions of the unaffected hemisphere and midline motor regions. While some activation was observed in the affected hemisphere of the stroke patients, it was restricted to the periphery of the damaged region. Because of its spatial resolution and noninvasiveness, fMRI can be used both to complement lesion studies in order to understand brain organization and to supplement lesion data in order to investigate functional changes associated with the lesions.

Thought question

What properties of fMRI may make it a poor choice for assessing function in patients with vascular lesions?

Probabilistic brain atlases

Up to this point, we have discussed two sources of structural damage to the brain: surgical excision of brain tissue, and focal lesions that make existing tissue nonviable. However, there are many other ways in which brain structure could change. Some diseases that affect the brain (e.g., Alzheimer's disease and schizophrenia) do not cause frank and focal lesions. Rather, regions within the brain of an afflicted individual may degenerate over the course of the illness. As with lesions due to stroke or surgery, volume loss in particular regions recovery of function The improvement in a previously impaired ability over time, due to functional or structural changes within the brain.
Figure 13.6 Variability in brain anatomy. These brain diagrams are overlaid with maps of variability in brain anatomy in the cortex of control and schizophrenic subjects (both males and females). Areas of high variability amongst individuals are shown in red-purple, while areas of low variability are shown in blue. Increased variability is observed in the frontal cortex for both male and female schizophrenics. (Courtesy of Drs. Katherine Narr and Arthur Toga, Laboratory of Neuroimaging, University of California, Los Angeles.)

may impair specific cognitive functions, and thus fMRI studies in these patient groups may be valuable as a prognostic indicator. Other aspects of brain structure, such as white matter integrity measured using DTI (see Chapters 5 and 11), or cortical thickness measured by anatomical MRI, may change during normal development. For example, the trajectory of change in cortical thickness can predict subsequent intelligence in children, as shown in a 2006 study by Shaw and colleagues.

New image processing techniques take advantage of large MRI databases and advanced computational methods to determine how variation in the structural properties of particular regions might predict disease states or brain function in individuals. Recall that in Chapter 8 we discussed how preprocessing fMRI data often involves the warping of the brains from individual subjects into a stereotaxic space to simplify statistical analyses across subjects. The degree to which a brain must be warped to match a normalized space might itself be of interest, because it provides a quantitative measure of regional brain variability. Investigators are using similar approaches to study structural differences between diseased and normal brains. Figure 13.6 illustrates the variability that can be found in brains of schizophrenic individuals compared with healthy control individuals. Note that the brains of the schizophrenic individuals show greater variability (red-purple colors) in several regions of the frontal lobes, including the midline. This finding corroborates results from many fMRI studies demonstrating that schizophrenic subjects show abnormal BOLD activation patterns in the prefrontal cortex, while performing a variety of tasks. Readers interested in learning more about the use of probabilistic brain atlases to study human disease are referred to the article by Toga and colleagues in the suggested readings.
Brain imaging and genomics

For a growing number of neurological and psychiatric disorders, researchers are discovering genetic variations, or **polymorphisms**, that are associated with increased risks of individuals developing those conditions. As researchers have begun to investigate the effects of these polymorphisms on brain function, a new field has emerged that has been named by Hariri and Weinberger as imaging genomics.

An early and notable study conducted by Bookheimer and colleagues in 2000 used fMRI to investigate memory processes in people with and without genetic risk factors for dementia. Thirty individuals were tested, all of whom were neurologically normal and had memory scores within the normal ranges for their ages. However, 16 of the individuals carried the epsilon 4 allele of the apolipoprotein E gene (APOE-4), which is associated with an increased risk of developing Alzheimer's disease. The remaining 14 individuals carried the epsilon 3 allele (APOE-3) and thus were not at increased risk. In an fMRI experiment that involved retrieval of items from memory, the APOE-4 group showed increased activation of the hippocampus, the parietal cortex, and the prefrontal cortex, compared with the levels of activation in the same regions in the APOE-3 group. These structures have been implicated as important to memory in many other experiments. When a subgroup of subjects participated in memory tests two years later, the decline in their memory performance was predicted by the degree of increased activation. That is, APOE-4 individuals who had increased fMRI activity in these regions were more likely to develop memory impairments. These results suggest that fMRI can be used to detect subtle patterns of damage that may result in later functional deficits, even before the functional impairments can be detected clinically. This study also points to the interesting possibility that increased fMRI activation may indicate compensatory processes that offset the functional consequences of the incipient disease.

More recent work has emphasized the potential role of particular neurotransmitter systems that may mediate diverse cognitive functions. As summarized in a 2006 review by Hariri and colleagues, there has been substantial interest in variation among individuals in the genes that control the synaptic reuptake of the neurotransmitter serotonin. A common paradigm involves scanning two groups of subjects using fMRI: those who possess alleles associated with higher synaptic concentrations of serotonin, and those who possess alleles associated with lower synaptic concentrations of serotonin. These different alleles have also been associated with phenotypic differences in traits like anxiety—high serotonin concentration predicts greater anxiety. Thus, many experiments have used stimuli that might evoke strong social or emotional responses (e.g., photographs of faces with different emotional expressions). In a number of studies, individuals with genetic variations that predict high synaptic concentrations of serotonin exhibited increased activation in the amygdala when shown photographs of emotional faces. This perhaps reflects the increased reactivity of that brain region to salient environmental cues in these individuals.

In summary, information about brain structure provided by stimulation, lesion, or TMS studies complements information about brain function provided by fMRI. Inferences made using one technique are improved by converging studies using other techniques. Questions about causality that are raised by fMRI results can be answered using lesion studies, just as fMRI can answer questions about large-scale systems and recovery of function that are

**polymorphism** A common variation in a gene or segment of DNA.
**imaging genomics** A new field that investigates the effect of genetic variation on brain structure and function.
raised by lesion data. Furthermore, fMRI can assess the functional consequences of individual differences in brain structure and genes. Therefore, techniques that examine the consequences of changes in neuronal activity will continue to be critical for research programs in cognitive neuroscience.

Measuring Brain Function

The first direct measurements of nervous system activity were obtained in 1848 by the German physiologist Emil Du Bois-Reymond, who discovered that nerves in a frog exhibit action potentials. Shortly afterwards, Hermann von Helmholtz used action potentials to measure the speed of conduction along the frog’s nerve. It is a scientific irony that Du Bois-Reymond and Helmholtz were both students of the physiologist Johannes Müller, who held the vitalist belief that activity of the nervous system was epiphenomenal and thus could not be measured experimentally. These early studies did much to explain neural transmission in peripheral nerves and muscle fibers. However, it was not until 1875 that the first electrical recordings of brain activity were published by the physician Richard Caton of Liverpool. Strongly influenced by the studies of his contemporary David Ferrier, Caton wanted to measure electrical potential changes in the cortex. Because these electrical changes were extremely weak, he used a reflecting galvanometer that had a mirror attached to its coils. As the voltage changed in the cortex of the animal subject, the position of the mirror moved very slightly, causing a visible change in the position of a reflected beam of light. This primitive amplification method made it possible to observe the very small voltage changes associated with brain activity. A half century later, the Austrian psychiatrist Hans Berger extended Caton’s work by measuring continuous changes in voltage on the scalp over time. The technique that he developed became known as electroencephalography, and its measurement became known as the electroencephalogram (EEG).

Many different electrophysiological methods exist for studying different facets of neuronal electrical activity, or electrogenesis (Box 13.1). At one extreme, these methods can measure changes in ion flow across isolated patches of a single neuron’s membrane, while at the other extreme, they can measure the synchronized activity of millions of neurons. We will begin our examination of direct measures of neuronal activity with a discussion of the recording of action potentials from individual neurons, a technique known as single-cell or single-unit recording. We will then discuss the recording of summated field potentials associated with postsynaptic activity. Field potentials can be measured in different ways at different scales, using both intracranial electrodes and scalp electrodes. We will conclude this section of the chapter with a consideration of magnetoencephalography (MEG), a technique that records the magnetic fields associated with neuronal activity.

**Single-unit recording**

The most direct measures of neuronal electrical activity characterize action potentials. The primitive methods used by Du Bois-Reymond to record the action potential in 1848 were greatly advanced by the introduction of the microelectrode in the first half of the twentieth century. Microelectrodes are placed either inside a neuron or next to the neuron’s cell body in the extracellular space. Studies measuring the rate of action potentials using microelectrodes, a technique known as single-unit recording, have generated some of the most important discoveries in all of neuroscience.
### BOX 13.1 Electrogenesis

In Chapter 6, we described the sequence of events associated with the depolarization of a small patch of the neuronal membrane. That discussion was in the context of the resulting demands for metabolites, the supply of which form the basis of the fMRI BOLD signal. Here we consider the electrophysiological consequences of membrane depolarization. Recall that the movement of ions through membrane channels supports information processing through the integrative and signaling activity of neurons. In this context, integrative activity refers to the total pattern of excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs) on the neuron's dendritic arbors and cell body. EPSPs and IPSPs vary in magnitude and duration depending on the strength and timing of the synaptic input. If the pattern of EPSPs and IPSPs can be considered a computation performed on a pattern of synaptic input, then the action potential is the output of this computation. Unlike postsynaptic potentials, action potentials are all-or-none; if the summation of EPSPs and IPSPs at the axon hillock surpasses a threshold, a self-propagating action potential will be triggered. But if the threshold is not surpassed, no action potential will occur. Because the action potential carries information to other interconnected neurons, we refer to action potentials as the signaling component of information processing in the brain.

What do we mean by electrophysiological? What properties of ions, membranes, and channels involve electricity? Atoms normally have as many negatively charged electrons as they have positively charged protons, and thus they are electrically neutral, having no net charge. However, if an atom gains or loses one or more electrons, it becomes an electrically charged ion. \( \text{Na}^+ \) is a positively charged sodium ion because it has lost an electron, while \( \text{Cl}^- \) is a negatively charged chlorine ion because it has gained an electron. Due to the selective permeability of a neuron's membrane and the action of ionic pumps, there is an unequal distribution of ions across the neuronal membrane and thus an unequal distribution of charge. An electrode placed inside a neuron at rest would record a large potential difference compared with an electrode outside the neuron, with the interior of the membrane about -70 mV relative to the outside.

Let's consider the sequence of events associated with the depolarization of a small patch of a neuron's membrane. First, there is an inward positive current caused by the inflow of positive sodium ions, creating a relative deficit in positive charge in the surrounding extracellular space. The depolarized patch of membrane thus becomes a **current sink** and attracts positively charged ions (Figure 1). The incoming positive charge flows within the neuron and away from the depolarized membrane, creating an intracellular accumulation of positive charge. This, in turn, causes an outward positive current from the unexcited portions of the neuronal membrane. This outward flow constitutes a **current source**, from which the positive ions flow back through the extracellular space toward the sink. To conserve charge, the efflux from the sink is an **ion** A charged atom.

**pump** A transport system that moves ions across a cell membrane against their concentration gradient.

**current sink** An attractor of positive ions. A depolarized patch of neuronal membrane is a current sink because positively charged ions will flow toward it.

**current source** A source of positive ions.

(continued on next page)
BOX 13.1 (continued)

source is equal to the influx at the sink. The strong current flow within the restricted intracellular space of the neuron is called the primary current, while the relatively weak return flow through the much larger extracellular conductive medium (or volume conductor) is called the volume current. While the primary current is confined to the intracellular space of the neuron, the volume currents extend throughout the conductive medium that contains the neuron.

The charge at the current source generates an electric field that is directed radially outward and whose strength decays with the inverse square of the distance from the source. That is, doubling the distance from the current source increases the area occupied by the electric field by a factor of four, and thus the intensity of the electric field is only one-fourth as strong. The charge at the current sink generates an electrical field that is directed radially inward.

Because the distance along the neuron between the source and sink is very small, we can idealize this close apposition of positive and negative point sources as a current dipole. The electric field produced by a dipole is simply the vector sums of the outward- and inward-oriented radial electric fields of the current source and sink. The electric field generated by the current dipole can be represented by a set of flux lines through the volume conductor that connect the point charges (Figure 2).

A potential difference can be measured in volts (or, more typically for electrophysiology, microvolts) between locations in the electric field. Isopotential lines, along which the voltage is constant, are analogous to the isocontours of a topographical map. The potential difference can be measured with a microelectrode inserted into the neuron.

**primary current** The current flow within a neuron caused by the inflow of ions through ion channels opened by synaptic activity.

**volume conductor** A continuously conductive medium. The brain, meninges, skull, and scalp constitute a volume conductor throughout which currents created by ionic flow can be measured.

**volume current** The return current through the extracellular medium that balances the primary current within a neuron.

**current dipole** A positive and negative point charge separated by an infinitesimal distance. A current dipole is used as a simple and convenient model for the electromagnetic fields produced by an activated neuron.

Figure 2. The extracellular electric field in the brain associated with neuronal activity. Shown is a representation of the consequences of the depolarization of the soma of a pyramidal cell. The volume currents are shown as solid isoflux lines, while the isopotential lines are dashed. The zero potential line occurs where the flux lines begin to bend inward toward the sink. Positive potentials are measured above the zero potential line and negative potentials are measured below. Note that the field weakens with increasing distance from the neuron. (After Cruetzfeldt, 1974.)
BOX 13.1 (continued)

stant, are perpendicular to the electric field lines. Because the charges at the source and sink are equal and opposite, the zero potential line is located at the point where the outward-directed field from the source begins to bend inward to the sink. The isopotential lines on the outward-directed side of the field measure positive voltages, while the isopotential lines on the inward-directed side of the field measure negative voltages. In the case of a depolarized neuron, the electric field produced by the source and sink can be measured by electrodes at different points in the extracellular space. For example, if depolarization occurred in the apical dendrites, then an electrode near the dendrites would record a negative potential relative to an electrode near the soma. If the soma were depolarized, as shown in Figure 2, the reverse would occur. The dipole is a convenient model for a depolarized neuron. Indeed, when observed from a distance, the fields generated by the coordinated activity of a larger assemblage of neurons can be modeled as though they were produced by a single equivalent dipole. This forms the basis for several of the techniques described later in this chapter.

In principle, the volume currents associated with neuronal depolarization can be detected anywhere within the volume conductor. Indeed, because the conductive medium around a neuron includes the entire brain and skull, neuronal activity can be detected with electrodes placed on the scalp.

apical dendrites The dendrites that are distant from the neuronal cell body. For typical pyramidal cells in the cortex, the apical dendrites extend to the superficial layers of cortex, while the cell bodies are located in deeper layers.

equivalent dipole A simplifying model that represents the electromagnetic field produced by a population of neurons as though it were produced by a single dipole.

The value of single-unit recording was powerfully demonstrated in studies initiated in the late 1950s by David Hubel and Torsten Wiesel, who were working at that time in the laboratory of Steven Kuffler at Johns Hopkins University. Using single-cell recording, Kuffler had previously demonstrated that retinal ganglion cells had a “center-surround” organization. That is, these cells increased their activity when a light was flashed in the center of a receptive field and decreased their activity when a light was flashed in the periphery of their receptive field. Hubel and Wiesel extended those studies into the visual cortex (Figure 13.7). By presenting more-complex stimuli, such as lines and edges, Hubel and Wiesel discovered that some cells in the primary visual cortex had receptive fields very different from those of retinal ganglion cells. Simple cells had a more rectangular receptive field that consisted of a central rectangular region with an excitatory response and rectangular regions above and below with an inhibitory response—as if these cells reflected the total output of a line of ganglion cells—and their rate of firing varied with the orientation of a visible line or edge. A similar approach was used to identify a second population of complex cells, which responded best to lines of a particular orientation, regardless of their position within the receptive field. Later studies built on this work to describe many important properties of the visual cortex, including its columnar arrangement and its changes during development. For these fundamental discoveries, Hubel and Wiesel received the Nobel Prize in Physiology or Medicine in 1981.

A more recent example of the value of single-unit recording in cognitive neuroscience comes from the work of Patricia Goldman-Rakic and her colleagues, who explored the properties of neurons in the monkey’s prefrontal cortex during an oculomotor delayed response task. Monkeys were required to remember the location of a visual target that was briefly presented in the peripheral field. The part of the visual field that, when stimulated, will result in an increase in firing of a particular neuron.

simple cell A neuron in the visual cortex that responds with increased firing to a stimulus with a preferred orientation in its receptive field, and with decreased firing to a stimulus in the region surrounding its receptive field.

complex cell A neuron in the visual cortex with a larger receptive field than a simple cell and that responds to a stimulus with preferred orientation anywhere within its receptive field.
Figure 13.7 Single-unit recording. This figure illustrates the recording of a simple cell from the visual cortex of the cat. (A) The cat views a slit of light, whose orientation is systematically varied. (B) The single-unit discharge is shown for each orientation. The preferred vertical orientation is indicated by the abrupt burst of action potentials for this stimulus. Some degree of generalization can be seen by the response of the cell to slightly off-vertical orientations.

Limitations of single-unit recording

Both the spatial and temporal resolution of single-unit recording are several orders of magnitude more precise than the resolution that can be obtained using fMRI. As can be appreciated from the above examples, single-unit recording can identify adjacent neurons that differ in their response properties (e.g.,
having different memory fields or responding to different aspects of a complex stimulus). In particular, the temporal resolution of single-unit recording is exquisite: each action potential of a neuron can be recorded as it occurs. Given these advantages, it is unsurprising that single-unit recording has made many outstanding contributions to neuroscience.

However, while the strengths of the single-unit recording technique far outweigh its weaknesses, the latter are still notable. Most significant is the fact that single-unit recording is an invasive technique that requires the brain to be penetrated by the recording electrode. Although single-unit recordings have been made on a limited basis in humans undergoing neurosurgery, this technique is primarily restricted to animals. A second limitation is that single-unit recording does not establish a causal relationship between the firing pattern of a neuron and the presumed underlying process. Thus, while it appears that the neuron represented in Figure 13.8 is coding one spatial location during working memory, the result demonstrates only a correlation. Would the removal of that single neuron render the animal incapable of remembering that specific spatial location? It is unlikely that working memory would be so dependent on a single neuron among the billions that constitute the monkey’s brain. Also, the challenges of identifying active neurons and tracking them over time limit most studies to collecting data from only a few tens of neurons, each of which was identified based on some criteria (e.g., changing firing rate in response to some experimental manipulation). Many other neurons within the same region might not respond to the particular stimuli used in an experiment, but could nevertheless support some important function.

One way to establish a causal relationship between a brain region and a cognitive construct under study is to disable the brain region and observe whether the process of interest can proceed without the participation of the neurons in that region. Techniques for disabling brain activity were discussed...
earlier in this chapter and include permanent or temporary brain lesions and transcranial magnetic stimulation. For example, many lesion studies in monkeys have firmly established that damage to the prefrontal cortex, whether permanent (e.g., caused by surgical lesions) or reversible (e.g., caused by local cooling or chemical agents), produces a selective deficit in working memory performance. Thus, the integration of converging data from single-unit recordings and lesion studies makes a much stronger case that these neurons play causal roles in working memory processes than the case made by either technique alone.

A second way to establish a causal relationship is to artificially control the firing of a neuron and observe its effect on behavior. Such an approach has been taken by Newsome and colleagues, who have used microstimulation to alter the output of neurons in the motion-sensitive visual cortex (MT/V5) in monkeys. Such neurons fire more frequently when a stimulus moves in one direction, which is often referred to as the “preferred direction” of the neuron, and thus their firing rate predicts the motion judgments expressed by the monkey. In a seminal 1994 study, Salzman and colleagues trained monkeys to perform a psychophysical task in which rewards were given for correctly indicating the direction of movement of a field of flickering dots. On most trials, dots with random motion were added to dilute the proportion of dots moving in a coordinated direction, making the task much more difficult. Yet, when electrical microstimulation was applied to neurons with the correct preferred direction, the monkeys’ performance improved. These data demonstrated that increased neuronal firing provides a code for direction preference that can cause monkeys to make particular judgments in a behavioral task.

Finally, while single-unit studies are difficult to conduct simultaneously with neuroimaging techniques like fMRI, research using both techniques can be conducted in parallel or in series. Some research programs now begin with exploratory fMRI studies that are followed by confirmatory single-unit studies. Others use human fMRI experiments to test hypotheses that were generated using single-unit recording. In addition, there has been increased interest in using fMRI in non-human primates as a potential bridge between these two techniques (see the discussion at the end of this chapter).

**Properties of electrical field potentials**

The term “field potential” refers to the summation of extracellular excitatory and inhibitory postsynaptic potentials. We shall use the shorthand PSP to refer collectively to **excitatory postsynaptic potentials** (EPSPs) and **inhibitory postsynaptic potentials** (IPSPs). Because the electrical activity of the neuron changes rapidly based on the strength and pattern of synaptic inputs, field potentials change rapidly to reflect this input. Thus, measurements of field potentials describe the underlying integrative neuronal activity with high temporal fidelity. Field potentials can be recorded by electrodes located anywhere within a conductive volume. Intracranial electrodes touch the cortical surface or penetrate deep structures within the brain, whereas extracranial electrodes rest on the surface of the intact scalp. Either type of electrode measures PSPs using similar principles, but the relative proximity of an electrode to the neuronal activity influences its sensitivity and spatial resolution.

Field potentials measured at these various spatial scales have provided useful complementary information for fMRI studies. However, it is the prospect of integrating scalp-recorded field potentials with fMRI measurements that has excited the greatest interest. It would be highly advantageous to combine

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**PSP** Any postsynaptic potential, excitatory or inhibitory, that results from synaptic activity.

**Excitatory postsynaptic potential (EPSP)** A depolarization of the postsynaptic cell membrane.

**Inhibitory postsynaptic potential (IPSP)** A hyperpolarization of the postsynaptic cell membrane.
Combining fMRI with other Techniques

Information about the sequence of neural events obtained using field potential recording with information about the location of neural activity provided by fMRI. This combination could potentially provide an unparalleled description of the spatiotemporal activity of neurons during cognitive tasks. Despite this promise, technical and theoretical limitations have slowed progress in achieving a fusion of these techniques.

Four facts about postsynaptic potentials are most critical for the following discussion. First, unlike the very brief (less than 1 ms) duration of a typical action potential, individual PSPs can be tens of milliseconds in duration. Second, hundreds or even thousands of synapses may make contact with the dendrites and soma of a single neuron, and PSPs can occur at many nearby synapses simultaneously. Third, as explained in Box 13.1, the volume current associated with an individual PSP extends into the extracellular space with a strength that diminishes rapidly with increasing distance from the source and sink. Fourth, the volume currents associated with individual PSPs combine in the extracellular space. Thus, the signal recorded by an electrode reflects the sum of all the PSPs produced at every synapse of every neuron in the brain, weighted according to their distance from the electrode.

However, the contribution of an individual PSP to a field potential is strongly influenced by the geometry and timing of its activity, such that an electrode will be much more sensitive to some aspects of activity than others. If all active neurons in a region have the same orientation and spatial arrangement, the extracellular volume currents they generate will combine to form a strong field. However, imagine that the neurons are geometrically rearranged so that alternating neurons are physically reversed in orientation. The activity of adjacent neurons would now have opposite polarity, and the resulting extracellular fields would be largely cancelled out. Cancellation could also occur if the dipoles had completely random orientations. The timing of the synaptic input to a population of neurons also affects the resulting extracellular field potential. If the synaptic input occurs at one time, as when activity is evoked by a sensory stimulus, then greater summation will occur than if the input is not synchronous. Thus, field potential recording is biased toward fields produced by synchronous inputs on regularly arranged neurons, such as those caused by simultaneous sensory input to a layer of pyramidal cells in the cortex. This synchronous activity often leads to oscillations in electrode voltage that are visible as regular waves in EEG recordings. These have been labeled according to their frequency bands (e.g., relaxation leads to activity in the Alpha band of about 10 Hz, while alert thinking leads to activity in the Beta band of 12-30 Hz).

Localizing the neural generators of field potentials

If an electrode placed anywhere in the brain will record the sum of all EPSPs and IPSPs of all synapses in the brain at any instant, how can field potential recording be used to localize active neurons? The answer is complex and relies on different biophysical concepts than those discussed for fMRI. Remember that field potentials are measured as the difference in voltage (or electrical potential) between pairs of electrodes. For intracranial electrode recordings, one electrode might be placed inside the brain while the second electrode might placed outside of the brain (e.g., on the scalp, chin, or earlobe). This external electrode is sometimes called the reference electrode, because it is relatively inactive compared with the electrode in the brain. In another arrangement, both electrodes may be placed inside the brain and the difference in their activity may be of interest. Regardless of the arrangement, the basic principles of
Figure 13.9  Localization of the generator of a field potential. Imagine that a stimulus evokes activity in a single ideal dipole located 5 cm below the skull's surface (isopotential, but not flux, lines are shown here). To locate the dipole, researchers lower an electrode along a vertical trajectory. A second electrode is placed on the earlobe to serve as a reference, and all measurements of potential difference, or voltage, are made between the electrode within the brain and this reference. On the first measurement, the electrode is lowered 4 cm into the brain, the stimulus is presented, and a waveform is measured with a peak potential difference of 100 μV. This single measurement is insufficient to localize the dipole. If the electrode is next raised 2 cm upward from this starting location so that it is now 2 cm deep, a potential difference of 25 μV is measured. Because the potential difference is smaller, the researchers conclude that they have moved the electrode farther away from the dipole. They reverse direction and move the electrode down 2.5 cm, to a position 4.5 cm into the brain. They now record a potential difference of 400 μV. By plotting their voltage measurements by distance, they recognize that the measurements follow an inverse square relationship and that the dipole must be located 5 cm deep. If the researchers lower their electrode past the zero isopotential line, an abrupt change in polarity occurs (indicated by the plots in green).

Field potential measurement are the same. Because the volume currents associated with PSPs extend throughout the conductive medium (i.e., brain, fluid, and scalp), the magnitude of the measured potential difference between two electrodes depends on the location of the dipole generator.

Although an electrode inside the brain might record a potential difference relative to a distant electrode outside the brain, there is no localizing information in that single measurement. From a single electrode pair, a nearby dipole generating a weak field cannot be distinguished from a distant dipole generating a very strong field. To localize the neuronal generator, one must make several measurements of the field to estimate its shape (Figure 13.9). The approach of localizing active neural tissue by mapping its electric field works well as long as there is only one spatially focal population of active neurons (i.e., one equivalent dipole). If several distinct populations of neurons are active (i.e., multiple equivalent dipoles), their electric fields overlap and their locations cannot be determined with certainty from the combined field. This is known as the inverse problem (Figure 13.10). However, due to the quadratic decay of electric field strength with distance, a given dipole will have very different effects on nearby electrodes but will contribute similarly (and weakly) to distant electrodes. Thus, to make inferences about the locations of the dipoles generating an electrical field, we need to sample that field using a large number of electrodes. Data collected using fMRI can play an important role in this process by identifying candidate areas of brain activation that may be possible sources of neuronal activity.

inverse problem The mathematical impossibility of determining the distribution of electrical sources within an object based on the measurement of electrical or magnetic fields at the surface of the object.

Intracranially recorded field potentials

At any instant, there are immeasurable numbers of current dipoles within the brain. The spontaneous fluctuation of field potentials caused by these dipoles gives rise to the electroencephalogram, or EEG, signal. However, most EEG activity will be unrelated to the processing of the particular sensory or cognitive events of interest and can therefore be considered as physiological noise.
This noise can be reduced by averaging many trials, which eliminates local field fluctuations that are not synchronized to the event of interest, leaving only the field potentials that are associated with the synchronizing event. The discussions in these sections focus on signal-averaged field potentials that are time-locked to a stimulus, or evoked potentials.

Evoked potential recordings have been used in many seminal studies of the sensory and motor organization of the brain. In the late 1930s, Clinton Woolsey and colleagues measured evoked potentials from electrodes placed on the surface of the sensory cortex (of cats and monkeys) to delineate its somatotopic organization. Although intracranial evoked potential mapping in animals has gradually given way to single-unit studies, it is still used in human studies today, usually in the context of epilepsy seizure monitoring or localization of function during neurosurgery. Intracranial recording has exceptional spatial and temporal resolution and thus can localize and record the timing of synaptic events associated with different populations of neurons (see Box 13.2 for an example). Using the techniques developed earlier by Allison and Wood, a 1997 study by Puce and colleagues compared evoked potential and fMRI techniques for localizing the hand region of the somatosensory cortex. The correspondence of localization by both techniques was quite good, suggesting that fMRI methods performed before surgery may provide similar information to cortical surface evoked potential studies performed during surgery. This conclusion was similar to that described earlier in the chapter for comparisons of direct cortical stimulation and fMRI. However, the coarse temporal resolution of the fMRI data meant that it could not be used to distinguish between separate populations of neurons within the somatosensory cortex, or determine the timing of synaptic events.

While the earliest field potential recordings using intracranial electrodes in humans investigated basic sensory processes, this technique has also been used to investigate human perception and cognition. When the eliciting event is considered to be a perceptual or cognitive event and not a simple sensory stimulus, the term event-related potential (ERP) is often applied. The deflections in the signal-averaged ERP waveform are known as ERP components, and they often have stereotypic latencies and distributions of voltage across electrode locations. One of the earliest ERP examples was reported by Sutton and colleagues in 1965, who presented subjects with simple auditory and visual stimuli that were either expected or unexpected based on cues presented shortly beforehand. When the
Because the volume currents associated with synaptic activity extend throughout the surrounding conductive medium, field potentials can be recorded deep inside the brain, on the surface of the cortex, or on the surface of the skull. However, because the volume currents are denser nearer to the active neurons, the spatial resolution of field potential measurement is greatest at nearby locations. In this box, we demonstrate how field potentials evoked by brief somatosensory stimulation to the median nerve at the wrist are manifest at different recording scales, including an array of penetrating electrodes in the monkey somatosensory cortex (Figure 1A), a surface array of electrodes on the human somatosensory cortex (Figure 1B), and an array of electrodes on the intact scalp of a human (Figure 1C).

Shown in the upper left panel of Figure 1A is a sagittal view of the central sulcus. The primary motor cortex (Brodmann area 4) is on the precentral bank of the central sulcus, while the primary sensory cortex is located on the posterior bank of the central sulcus (area 3b) and the crown of the postcentral gyrus (area 1). The neurons in area 3b are oriented tangentially, or horizontally, to the cortical surface, with their apical dendrites oriented anteriorly in the direction of area 4. The neurons in area 1 are oriented radially, or vertically, with their apical dendrites oriented upwards toward the crown of the postcentral gyrus. The dots in this panel indicate locations from which field potential measurements were made. The color contour maps indicate the distribution of voltages at seven different time points after the stimulus was presented.

At 9 ms after a brief stimulation to the median nerve of the arm, the cell bodies of the area 3b somatosensory neurons have already become depolarized.
BOX 13.2 (continued)

ized (cool colors) while the apical dendrites become polarized (hot colors). The tangential orientation of this dipolar field is made obvious by the close horizontal apposition of the red and purple blobs. By 13 ms, the cell bodies in the area 1 somatosensory neurons become depolarized. This creates a vertically oriented dipole, with positive voltages recorded directly above the crown of the postcentral gyrus and negative voltages recorded below. This radial dipole begins to fade by 17 ms. However, at 17 ms, the activation of the area 3b neurons now extends to the apical dendrites. The sink–source relationship between the apical dendrites and the soma now reverses, and the polarity of the field reverses. The reversal of the field can be appreciated by comparing the positions of the hot and cool colors at 10 and 20 ms.

This same sequence of events can be observed in field potential recordings from the cortical surface, as shown in Figure 1B. These recordings were made with electrode arrays similar to that shown in Figure 13.2. Unlike the monkey electrodes, which penetrate the brain in columns, these electrodes in the human brain are lying on the surface. The anterior brain is to the left in each panel. Because of the larger size of the human brain, the initial depolarization of the cell bodies of the somatosensory neurons in area 3b occurs with a latency of about 20 ms, at which time a positive current flows from the source in the apical dendrites to the sink in the cell body. This is recorded as a positive evoked potential (called a P20) at the level of the apical dendrites and anterior electrode locations. A negative evoked potential (N20) is simultaneously recorded at the level of the soma and at posterior electrode locations. The neurons in area 1 are activated about 5 ms later, at which time a positive evoked potential (P25) is recorded directly above their apical dendrites. This occurs somewhat medially to the main axis of the area 3b dipole. And, as in the monkey, the field generated by the 3b neurons reverses polarity, as is evident at 30 ms. Finally, the same sequence of events can be recorded with electrodes placed on the scalp surface, as indicated in Figure 1C.

These cortical and scalp recordings demonstrate some facts about localizing neurons from field potential maps. As in our simple example in Figure 1, the actual location of the area 3b neurons is marked by the iso-potential line. Because these neurons are oriented horizontally, the largest positive and negative fields are located to the anterior and posterior, respectively, of the active neurons. Thus, it is the shape of the field and not its maximum amplitude that is used to localize the area 3b neurons. This situation is different for the radially oriented area 1 neurons. As their associated dipolar field is oriented vertically, the neurons are located directly below the maximum field potential. Thus, the shape and orientation of the dipolar fields are important in localizing the active neurons.

subjects experienced an unexpected stimulus, there was a systematic positive deflection in the EEG waveform that peaked about 300 ms following stimulus presentation. That has since been labeled the P300 (or P3) response. In subsequent years, there have been literally thousands of electrophysiological studies investigating the properties of this component. More recently, fMRI researchers using similar paradigms have identified regions of the prefrontal and parietal cortex, among others, whose activations increase in response to unexpected events. As shown in a 2004 study by Bledowski and colleagues, distinct sets of brain regions may support different aspects of the P300 response: regions of the parietal and temporal cortex may contribute to P300s evoked by task-irrelevant events, whereas regions of the prefrontal and insular cortex may contribute to P300s evoked by unexpected events that require immediate action.

Higher perceptual processes have been investigated by Allison and colleagues, who measured ERPs from intracranial electrodes within the areas of the ventral occipitotemporal lobe associated with complex vision. In their studies, patients were shown pictures of many different types of objects, including faces, flowers, words, and scrambled objects that maintained their low-level visual properties but were unrecognizable. Faces, but not other stimulus categories, evoked focal ERPs from the surface of the fusiform gyrus (Figure 13.11). Direct
cortical stimulation of the same region produced transient prosopagnosia and face hallucinations in some patients. In 1997, Puce and colleagues compared the location of this face-specific region to that identified by fMRI. The study was conducted by performing both procedures in each of two patients, although not simultaneously. Good correspondence was obtained between the location of the face-specific ERPs and fMRI activation by faces. So, if we know that fMRI and ERP activity are both present in a brain region, how can we know which of the sequence of field potentials measured in that location contribute to the BOLD signal? Note that electrodes within the fusiform gyrus revealed several sorts of field potentials. Early in processing is observed a face-specific potential, known as the N200, that reflects a negative change in polarity about 200 ms after stimulus onset. This early response may share some neural generators with a component known as the N170 that is measured using scalp-related ERPs. There are also later and long-lasting face-specific changes in the ERP signal that occur after about 600 to 800 ms; the onset of this activity can be seen in Figure 13.11B for Electrode 10. One possible interpretation for these two forms of activity is that the early potential reflects the initial perceptual processing of the face, while the later potential represents recurrent or feedback influences from higher brain regions. Under this idea, different functional processes are not separated in space but are separated in time.

To evaluate whether this model of fusiform function is correct, one must manipulate some aspect of the stimulus that would affect one functional process but not the other. For example, recognition of a face may be supported by completely different brain regions, but the results of that distant processing may modulate the activation of the fusiform gyrus. So, an experimenter could manipulate such things as the identities of presented faces, attention to face identity, or memory of face identity. If the fMRI activation in the fusiform gyrus reflects the later potential, then variation in face identity may cause changes in the BOLD signal and in the later evoked potential, but not in the N200. Because a psychological construct may be associated with some aspects of neural activity (e.g., BOLD signal change) but not others (e.g., the N200), converging operations are critical. For example, a researcher who observes an fMRI response in the fusiform gyrus to judgments of face identity might infer that this response reflects neuronal activity at the time of the most prominent face-specific ERP, that is, at 200 ms. Thus, fMRI data considered in isolation may lead to the premature conclusion that judgments of face identity occur early in time within the fusiform gyrus. Although hypothetical, this example reflects current debates concerning the sequence of events associated with face processing in the brain, including the effects of directed attention, face memory, and emotional face expression. Since great care must be taken in interpreting the timing of events when only fMRI evidence is available, intracranial electrode recordings can provide an important complementary source of information.

**Scalp-recorded field potentials**

Because the skull and scalp are conductive, the field potentials generated in the brain can also be recorded from arrays of electrodes placed on the scalp. Unlike intracranial field potential studies, which can only be conducted within a limited clinical context, extracranial (or scalp-recorded)
field potential studies are conducted with normal volunteer subjects in hundreds of laboratories around the world. The electrodes are placed at standard locations on the scalp surface, either one at a time using adhesives or via a stretch cap with electrodes at standard locations (Figure 13.12). A typical electrode cap might include 64 electrodes, although some may have 128 or more.

Researchers are interested in identifying ERP components that are associated with various aspects of language comprehension, memory, executive processing, attention, face perception, and dozens of other processes. Based on these components, researchers have developed process models that take advantage of the high temporal resolution of ERPs to predict the sequences of functional operations that occur during complex behaviors. As we noted in our introduction to cognitive neuroscience earlier in this chapter, these process models may have considerable value for understanding cognition, even if information is lacking about where these operations occur within the brain. This makes ERP recording a valuable tool for cognitive neuroscience research.
BOX 13.3 Combining fMRI and EEG/ERP techniques

All methods for noninvasively measuring brain activity in humans, including fMRI, have advantages and disadvantages. As noted throughout this textbook, a strength of fMRI is its excellent spatial resolution, which allows the identification of activated regions with better than a one-centimeter resolution. Yet, fMRI only provides temporal resolution on the order of seconds. Since many aspects of neuronal activity occur much more rapidly, on the order of a few tens of milliseconds, fMRI data contains relatively limited information about the sequences of the underlying neuronal events (see Chapter 7 for examples). In contrast, electrical recording techniques such as the measurement of event-related potentials (ERPs) or examining changes in the power frequency of the electroencephalogram (EEG), can resolve changes in evoked brain activity with millisecond precision, but give only coarse information about the spatial distribution of that activity. Because fMRI and ERP/EEG techniques have largely complementary strengths and limitations, combining these methods may provide a more comprehensive picture of brain function (see Figure 1 for an example).

There are two primary approaches for combining these techniques: parallel EEG-fMRI and simultaneous EEG-fMRI. Parallel studies generally involve the collection of data sequentially, using both methods in the same subjects performing the same tasks, usually in an event-related design. For an example, see the 2005 article by Busse and colleagues cited in the references. Most studies use relatively rapid event-related designs, so that there is sufficient power to identify effects associated with each event type. This can introduce problematic overlap between the neural responses evoked by successive stimuli, both because of the sluggishness of the hemodynamic response and the latency of some ERP components. To mitigate the response overlap, researchers typically randomize stimuli and use algorithms that can extract the response associated with one event within a rapid sequence. Note that similar sorts of procedures underlie fast event-related fMRI analyses more generally. The fMRI data provide information about the locations of activation that can improve the spatial inferences drawn from EEG data. In most such studies, the clusters of significant fMRI activation define a set of possible sources for the observed ERP effects. These a priori constraints substantially increase the likelihood that the source analysis algorithms will converge on an accurate solution. While parallel EEG-fMRI studies have made many advancements, they have intrinsic limitations. They assume that the extracted brain activity recorded in the separate sessions reflects reasonably similar cognitive processes. Furthermore, they only allow researchers to draw conclusions about average activity observed during performance of a task, but not about trial-to-trial variation in activity.

Potentially more powerful is the simultaneous collection of ERP/EEG and fMRI data. This provides the ability to compare directly the fMRI activation and ERP activity evoked by each event—greatly increasing the power of comparisons between these different types of data. The primary disadvantages of simultaneous EEG-fMRI studies are technical. All electrodes and wires must be MR compatible and the electrode cap must be comfortable enough (and small enough) for extended wear in the confined space of the MR scanner. Placing electrodes on the surface of the scalp can cause artifacts in the MR images. And, the rapidly changing currents in the MR gradient coils induce electric currents in the ERP recording hardware, which in turn cause large and problematic artifacts in the recorded electrophysiological signal. One approach for minimizing these artifacts is clustered (or sparse) acquisition. This involves collecting the fMRI data dur-

**forward solution** The direct calculation of the electric and magnetic fields that would occur at an array of sensors based on a given distribution of dipoles with known orientations and magnitudes.

Given the topic of this textbook, our discussion of scalp ERPs is motivated by their potential for complementing fMRI studies. See Box 13.3 for an extended discussion of the technical and conceptual challenges of combining these techniques. If we know the precise spatial configuration and strength of the equivalent dipoles active at a particular instant, then it is possible to compute the exact scalp distribution of potential that would result. This mathematically tractable process is known as the forward solution. Furthermore, the temporal sequence of neuronal events, even those separated by mere milliseconds, changes the scalp distribution of the electric fields in predictable ways. If fMRI can tell us the exact location of all brain regions activated by a stimulus, if we
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BOX 13.3 (continued)

Figure 1 Simultaneous acquisition of fMRI and ERP data in a cognitive experiment. Subjects performed a response incompatibility task in which they had to respond with a left or right button press according to the direction of an arrow in the middle of a screen. In half of the trials, that arrow was preceded 80 ms earlier by an arrow cue pointing in the same direction (compatible condition), while in the other half of the trials, the arrow cue pointed in the opposite direction (incompatible condition). (A) Compared with correct responses, errors on incompatible trials evoked a centrally located ERP component whose peak occurred shortly after the button press. (B) The estimated source generator of the ERP was the anterior cingulate gyrus (red circle; tail indicates dipole direction). (C) The authors then used the amplitude of the ERP response on each trial to predict the amplitude of the fMRI hemodynamic response. They found a significant correlation with voxels in the anterior cingulate gyrus (shown in two views), thus providing strong and converging evidence that this region was associated with task performance. (After Debener et al., 2005.)

...ing part of the TR, which is typically made somewhat longer, leaving an open period when the gradients are not changing and the electrophysiological data can be acquired without artifacts. Alternatively, filtering algorithms can estimate and remove the artifactual activity. Another challenge comes from the effects of physiological noise: pulsations associated with blood flow can cause movement of the EEG electrodes inside the magnetic field of the scanner. Although these technical complexities of the simultaneous-recording approach have thus far limited its application and thus its impact, these difficulties are steadily being overcome. Accordingly, the simultaneous-recording approach is becoming more practical and will undoubtedly make major contributions to the field of cognitive neuroscience.

know the orientation of the active neurons in those regions, and if we know the precise time course of activity in those regions, then we should be able to calculate the resulting scalp electric fields using forward solution techniques.

While this would be an impressive technical feat, its successful implementation depends on us already knowing everything about the spatiotemporal sequence of neuronal activity. What if you measured the electric field at the scalp? Could you then calculate the spatial configuration of neural generators and the temporal sequence of their activation? This reverse operation, computing the spatial configuration of dipoles from knowledge of the scalp distribution of voltage, is known as the inverse problem, introduced previously. If
the inverse problem could be solved, the need for localizing techniques like fMRI would be greatly reduced, as scalp-recorded ERP studies would provide complete information about both temporal and spatial properties of neuronal activity. If we know for certain that only one dipole is active, we can solve for its location from an adequate sample of its potential distribution on the scalp. However, in the more likely event that many dipoles are simultaneously active, this approach will not work, because different configurations of dipoles can create the same distribution of voltage at the scalp. Thus, the inverse problem has no unique solution.

The inverse problem applies to all field potential recording, not just scalp ERPs. However, in intracranial recording we can move our electrode so close to the active neurons that the contributions from distant dipoles are negligible — making it appear as if only one equivalent dipole is active at each electrode. For scalp recording, all electrodes on the scalp are, in essence, distant from all dipoles in the brain. This problem is compounded by the presence of the skull, which has a much higher electrical resistance than the brain and greatly reduces the spatial resolution of scalp-recorded ERPs. Even though no algorithm can provide a unique solution to the inverse problem, many powerful techniques have been developed to create approximate solutions by incorporating simplifying assumptions. Readers interested in additional details on this topic are directed to the paper by Baillet and colleagues listed in the suggested readings.

What if the spatial configuration of dipoles was known in advance? Under such conditions it would be possible to use the scalp ERP data to estimate the temporal changes in the strength of those dipoles and thus generate a time course of activity for each brain region. It has been asserted that fMRI activations may be used to provide the locations of the dipole generators, and thus scalp-recorded ERPs could provide information about the dipole time courses. In 1998, the validity of this approach was tested by Liu and colleagues using Monte Carlo simulations. Their modeling attempted to account for two potential problems in combining fMRI and electrophysiological measurement: that some active neural generators would not be represented by an fMRI activation, and that an fMRI activation might not be associated with neural activity. The results of their simulations were encouraging, and the authors suggested that fMRI might be useful for seeding models of dipole structure.

**Magnetoencephalography**

In the prior section on field potentials, we explained how electrophysiological methods could be used to localize neuronal activity by measuring electrical field potentials. A current flowing through space gives rise to both an electric field and a magnetic field. The neuroscience technique for measuring these magnetic fields is magnetoencephalography, or MEG. The magnetic signals produced by neuronal activity are extremely weak, on the order of 100 femtoTesla or fT (an fT is \(10^{-15}\) Tesla). To record these weak fields, MEG scanners use very sensitive coils known as superconducting quantum interference devices, or SQUIDs, that detect magnetic flux. In early studies, a single SQUID sensor attached to a gantry was moved systematically over the skull to make sequential measurements of the magnetic flux. In modern MEG systems, hundreds of sensors are housed in a helmetlike device and measurements are made simultaneously (Figure 13.13).

Despite the difference in instrumentation, MEG studies are very similar in practice to scalp-recorded electric field potential studies (i.e., both EEG and ERPs). Just as ERPs can be obtained by time-locked averaging of the EEG waveform, **evoked magnetic fields**, or EMFs, can be identified by time-locked averaging of the MEG waveform. Moreover, MEG recording has a significant advan-

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**Evoked magnetic fields (EMFs)** A change in the MEG signal that occurs in response to a particular stimulus. An EMF is the magnetic equivalent of an evoked potential or event-related potential in EEG.
tage compared with scalp-recorded ERPs; because magnetic fields are unimpeded by the high resistance of the skull, they can be measured with higher spatial resolution than electric fields. In that sense, MEG and EMF measurements are more similar to direct cortical recordings than to scalp recordings, although MEG is not immune to the inverse problem.

Unlike electrophysiological methods that depend on volume currents, MEG depends mainly on the primary current that extends along the long axis of the neuron and is very sensitive to the neuron’s orientation. In a spherical medium, like that approximated by the skull, the magnetic fields generated by a radially oriented dipole cannot be detected outside of the head. Thus, if the primary current does not have a component that is tangential to the surface of the skull, it cannot be detected by MEG. This can be both an advantage and a disadvantage. It is an advantage in that radially oriented neuronal populations can be ignored in modeling the generators of magnetic fields, and thus the models are simpler. It is a disadvantage in that MEG does not provide a complete description of neuronal activity (e.g., it is largely insensitive to activity in neurons at the top of gyri). For this reason, MEG and EEG measurements are often obtained simultaneously.

Figure 13.13 Magnetoencephalography (MEG). (A) Shown is a modern MEG system with 248 MEG sensors plus additional channels for noise reduction and simultaneous EEG recording. The sensors are located in the helmet close to the subject’s head. The SQUID sensor devices require cryogenics contained in the large thermos-like dewar to maintain superconductivity. (B) Just as an electrical current in a wire creates a circular magnetic field, dendritic currents in the cortex produce circular magnetic fields that can penetrate the scalp. The fields most easily measured are generated by neurons in the sulci, because those fields penetrate the scalp and can be detected by a magnetometer outside the skull. Conversely, fields generated by neurons in gyri tend to be parallel to the scalp and thus are more difficult to detect. (C) By placing those magnetometer sensors adjacent to the scalp, the highly sensitive detector coils can identify the changing magnetic flux from active neurons that penetrates the skull. (D) By placing those magnetometer sensors adjacent to the scalp, the highly sensitive detector coils can identify the changing magnetic flux from active neurons that penetrates the skull. (D) Distribution of the magnetic fields over the head of a normal subject, showing the changes in field strength evoked by an auditory stimulus around 100 ms after its presentation (i.e., the M100 component). The MR image in the right panel shows the estimated location of the source neurons derived by dipole source analysis. (A, courtesy of Dr. Ken Squires, 4D Neuroimaging; D after Woldorff et al., 1999.)
Similar strategies have been advanced for combining EMF and fMRI studies as have been developed for combining ERP and fMRI. For example, a 1999 study by Ahlfors and colleagues combined fMRI with MEG to examine the neural response to a sudden change in perceived motion. They used fMRI to identify several regions within the visual cortex: the primary (V1) and secondary (V2) visual cortices, and a motion sensitive area (MT+). The fMRI-derived location of the MT+ activation matched that of the peak EMF response during a time range of 130 to 170 ms and again at about 260 ms. In contrast, EMF responses from V1 and V2 were very small, with peak activities at about 200 to 260 ms. As these activations were longer in latency than the initial activity for area MT+, they may reflect feedback from other areas. This latter conclusion, based on the EMFs, is important, because fMRI data alone suggest that activity in V1 and V2 may be early in the anatomical sequence of motion processing.

To date, relatively few studies combine measurements of EMFs or ERPs with fMRI. However, despite the significant obstacles related to ambiguities in dipole modeling solutions, the addition of fMRI data to constrain the modeling of neural generators and to infer their time courses of activation holds much promise. The temporal ordering of neuronal activity in a widespread pattern of fMRI activations would be a tremendous leap forward in the modeling of complex sensory, motor, and cognitive tasks.

Using fMRI with non-human primates

The fMRI studies described so far in this book have been restricted to human subjects. Yet in principle, other animals could serve as research subjects. Within the past few years, a handful of laboratories have begun fMRI studies of non-human primates, primarily monkeys (e.g., the rhesus macaque, Macaca mulatta). Although fMRI is not necessary for the in vivo study of the animal brain, given the power of intracranial electrophysiology, it does provide some important advantages (see the commentary written by Paradiso in 1999 for additional discussion). First, and most importantly, it can link human and animal research. In all fields of science, technical advances can cause divisions that are based on methodology rather than topic. Researchers who conduct electrophysiological studies of decision making in monkeys may communicate with other monkey electrophysiologists but not with researchers using human neuroimaging. Studies using fMRI in monkeys can bridge the gap between human fMRI and monkey electrophysiology, allowing their results to be more easily integrated. This may be particularly important for topics like vision, whose basic neural organization was established primarily using animal electrophysiology.

Second, the use of fMRI in animals provides information that can compensate for the limitations of other techniques. In many ways, intracranial electrophysiology is considered to provide the clearest evidence for the function of a brain region, in that implanted electrodes can provide direct information about neuronal activity. However, each electrode records activity from only a small brain region (in some cases a single neuron), and therefore a breadth of spatial coverage is sacrificed. Using fMRI to guide subsequent electrode placement could substantially improve the efficiency of electrophysiological research. And, since fMRI does not require surgery (e.g., to implant electrodes), it may have some ethical advantages for some forms of exploratory research.

Third, animal fMRI studies can inform human fMRI work, even though both brain anatomy and cognitive function differ between species. More data can be collected in animal fMRI studies than is typical in human research, given
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that the same animal could participate in a large number of experimental sessions. Thus, functional SNR could potentially be much higher in animal fMRI, benefiting studies with more experimental conditions or with parametric changes in an independent variable. Using fMRI in monkeys also provides an opportunity to introduce other concurrent manipulations, such as simultaneous electrophysiological recording, use of contrast agents, or evaluation of drug effects. While these manipulations may not be practical in human volunteers, they may be conducted under the guidelines for acceptable care and use of laboratory animals.

The first studies using fMRI in nonhuman primates were published in 1998 by two groups who simultaneously conducted very similar experiments. Stefanacci and colleagues recorded fMRI BOLD data from the visual cortex of a rhesus monkey during a passive viewing task. The animal lay in a prone (or "sphinx") position within a specially designed apparatus, which was itself contained within a local gradient coil inside a standard clinical 1.5-T MRI scanner (Figure 13.14). The animal's head was fixed into place using a head post, so that it could look down the scanner bore at a display screen. A mock scanner was used over a period of a month to familiarize the monkey with the confinement and noise levels of the scanner. During the scanning sessions, the monkey watched a video movie that was presented in a 16 s on/16 s off blocked design. The monkey also periodically received a squirt of juice as a reward for staying still during the session. Using scanning procedures similar to those

Figure 13.14 Collecting fMRI data in the monkey. Using fMRI with nonhuman animals poses problems, particularly when they are awake and performing a task. This figure shows one of the first successful fMRI experiments with monkeys. A rhesus macaque monkey was placed in a special primate chair that was turned sideways to fit into the bore of a standard human 1.5-T scanner (top). The animal watched a movie presented in a blocked on/off design. Significant BOLD activity was found in the temporal (A) and occipital (B) lobes. Researchers noted that there were substantial problems with head motion, due in part to the use of scanning and restraint hardware that were not designed specifically for monkeys. (From Stefanacci et al., 1998.)
used in human studies, the authors found significant activation in occipital visual regions, as well as in higher visual regions within the superior temporal gyrus. Another study by Dubowitz and colleagues used a similar apparatus and visual stimulation paradigm. Their results mirrored those of Stefanacci and colleagues, in that they were able to identify regions of significant activity in the visual cortex.

Though highly exploratory, these early studies demonstrated the feasibility of collecting BOLD fMRI data in monkeys. Subsequent studies from these groups and others have replicated the results, while suggesting topics for future research. One area that holds particular promise is the use of exogenous contrast agents to increase SNR. Recall from Chapter 7 that injection of a highly paramagnetic substance into the bloodstream causes susceptibility-related signal loss on T₂*-weighted images. Because the magnitude of this signal loss depends on the total amount of the contrast agent that is present in a voxel, it serves as an index of local cerebral blood volume. While exogenous contrast agents are not practical for most human fMRI studies given the noninvasiveness of standard BOLD measurement, they may offer significant advantages for studies in nonhuman animals. As an example, a 2002 study by Leite and colleagues demonstrated that the use of an exogenous contrast agent (monocrystalline iron oxide nanoparticles, or MIONs) increased functional sensitivity by a factor of two to three over BOLD contrast, depending on the experimental design.

Another important research area is the use of animal fMRI models to improve understanding of the basic principles of BOLD fMRI. In a series of experiments, Logothetis and colleagues have investigated the relationship between hemodynamic and electrophysiological measures of brain activity, using concurrent fMRI and ERP/EEG measurements. We have discussed the results of these studies in detail in Chapter 7, but one of their technical advances is illustrated here, namely a custom vertical-bore MRI scanner designed specifically for use with monkeys (Figure 13.15). Several other institutions have installed monkey-specific scanners in recent years.

Although nearly all fMRI studies in monkeys have explored basic sensory functioning, studies of more-advanced cognitive processes are also possible.

![Figure 13.15](A) A custom MRI scanner for monkey studies. (A) Through the creation of hardware specific for studies of nonhuman animals, the quality of fMRI data can be greatly improved. Logothetis and colleagues have created a custom scanner that allows the animal to remain upright with the head restrained (B). (Courtesy of Dr. Nikos Logothetis, Max Planck Institute, Tübingen, Germany.)
a very interesting study of executive function published in 2002, Nakahara and colleagues investigated the brain regions involved in shifting between response sets. An important hallmark of human prefrontal cortex damage is an inability to shift from one mode of responding to another, as demonstrated by behavioral impairments in the Wisconsin Card Sorting Test. In order to study set shifting in monkeys, Nakahara and colleagues developed a modified version of this test that two macaque monkeys (*Macaca fuscata*) performed within a standard clinical scanner. The authors found significant activity in response to category shifts in the monkeys' inferior prefrontal cortex, as well as in the intraparietal sulcus, posterior cingulate, precuneus, and insula. They then compared these regions of activity with those from an identical fMRI experiment conducted in humans (Figure 13.16). The authors found that the humans also showed significant activity in the inferior prefrontal cortex, in a region with similar cytoarchitectonic properties as those identified in monkeys. Future studies of this type will be critical for comparing maps of brain function between species.

The use of fMRI in nonhuman animals has considerable potential, but it also presents a new set of challenges. In a sense, it combines all of the problems of fMRI with all of the problems of animal studies. One difficulty that must be overcome is subject motivation. Human fMRI subjects may be motivated by several factors: the desire to help the experimenter, a sense of purpose in helping to advance science, or the thought of the payment they will receive upon completion of the study. In contrast, animal subjects are more motivated by the direct rewards given for experimental compliance, such as squirts of juice. Though juice is a good reward system for behavioral studies, it is not ideal for fMRI. Swallowing a sip of juice requires the contraction of muscles in the jaw and throat, which in turn causes both distortions in the local magnetic field and head motion. Even with a periodic reward, an animal may have difficulty remaining still. For example, in the study by Stefanacci and colleagues, a number of the experimental runs were severely corrupted by large head motions.

Figure 13.16 Comparison of fMRI data from monkeys and humans. A potentially exciting use of fMRI in monkeys is the direct comparison with human data. Data were collected from both macaque monkeys (A) and humans (B) in a variant of the Wisconsin Card Sorting Test (height of slices, z, shown in mm). In both species, there was significant activity in the bilateral inferior frontal cortex in response to stimuli that required a shift from one response set to another. This result suggests that these regions may be functionally homologous between the species. Note that the brain images are shown at different scales; the human brain has more than ten times the volume of the macaque brain. (After Nakahara et al., 2002.)
The authors noted that this head motion may have been exacerbated by the limitations of using a clinical MRI scanner with a primate chair inserted within the bore, so dedicated monkey scanners have the potential to minimize such problems.

Finally, we note that animal models themselves have limitations. Monkeys are similar to humans in overall brain organization, but they are expensive to maintain and test, and relatively few institutions have large colonies. A less expensive option is to use rodents, as is typical for behavioral neuroscientific studies. Rats are cheap, common, and perform many tasks well, but they have extremely small brains (about 2 cc). Most genetic manipulations have been performed in mice, making them good candidates for studies of the effects of specific genes on brain function, but their brains are smaller still (about 0.4 cc). To emphasize the problem of scale involved with imaging a rodent brain, consider that with a voxel size typical for human studies, only about 30 voxels would be needed to contain the entire brain of a rat, and only about 6 would be needed for the brain of a mouse. Yet despite these limitations, several fMRI studies in rodents have been conducted using ultra-high-field scanners. These studies have generated exquisite maps of sensory cortices, as exemplified by an image of the olfactory bulb of a rat produced by Xu and colleagues. Thus, fMRI studies of nonhuman primates and other animals are likely to become increasingly important, both for improving our understanding of brain function and for clarifying the basic physiological mechanisms of fMRI.

Summary
The field of cognitive neuroscience is growing rapidly and accruing a broad range of experimental observations. In part, this reflects the vitality of a young field that has only recently gained access to new and powerful techniques like fMRI. However, the continued maturation of cognitive neuroscience will require more than observations—it will require new theoretical frameworks based on convergent data from many methods. Two classes of techniques are used by cognitive neuroscientists. The first class includes approaches that manipulate brain function, such as direct cortical stimulation, TMS, genetics, and lesion studies. These techniques can guide inferences about the necessity of a brain region for a given cognitive process, providing important complementary evidence for fMRI studies. The second class includes approaches that measure brain function, notably electrophysiological studies of single-unit activity, local electrical field potentials, and local magnetic field changes (along with neuroimaging techniques like PET and fMRI). These electrophysiological approaches provide better temporal resolution than fMRI but have problems with localization of neuronal generators. Combined fMRI and electrophysiological studies thus show promise for improving functional resolution, although many technical challenges remain. Researchers should choose their experimental strategies, including techniques and experimental designs, according to their research questions. This interdisciplinary approach is the future of cognitive neuroscience, and indeed of all of science.

Suggested Readings
to the physiology of field potentials with a philosophical consideration of their use in localizing sensory, motor, and cognitive function.


*Indicates a reference that is a suggested reading in the field and is also cited in this chapter.

Chapter References


Introduction

On November 11, 2007, the New York Times published an article that examined how uncommitted voters responded to images of candidates for the United States President. Although the 2008 presidential election was still a year away, the character of the campaign had already taken shape. The top candidates were already well known to the electorate through debates and advertisements. The core issues—the Iraq war, the economy, and health care—were central in the minds of voters. Moreover, immeasurable reams of newsprint had already been dedicated to analyses of voter attitudes and behavior. Against this noisy background, a single article (even in as prestigious a news outlet as the New York Times) would barely be noticed. Yet, this story was an immediate hit. It became the most emailed article from the Times, while engendering immediate celebrations and rebuttals from many other news sources. In speculating why the article—labeled as an opinion/editorial piece—became so controversial, one should begin with its title: “This is Your Brain on Politics.”

Authored by neuroscientists, political scientists, and applied fMRI researchers, the article described an fMRI experiment in which 20 potential voters viewed images and videos of leading candidates. (The details of the design were not provided in the Times article, but they are not critical for this brief summary.) Based on the patterns of activation evoked by different candidates, the authors made inferences about the emotional and cognitive attitudes that could drive voting behavior; for example, “Videos of McCain and Obama indicated a notable lack of any powerful reactions, positive or negative,” “Rudy Giuliani versus Fred Thompson: the latter evokes more empathy,” and “Emotions about Hillary Clinton are mixed.” In support of this last conclusion, voters who reported disliking Clinton showed increased activation in the anterior cingulate cortex, a region often associated with behavioral conflict. Accompanying the article was a multimedia slide show that displayed attractively rendered three-dimensional brains, with the functional associations of the activated regions helpfully labeled (e.g., “conflict”).

Rarely has a single news story so clearly highlighted both the promise and limitations of fMRI. Imagine a similar story that made inferences from polling data, or from a survey of a small, single-interest group. Would it be newsworthy that Hillary Clinton, one of the more polarizing figures of recent U.S. pol-